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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/714,882	11/16/2000	C. Alexander Turner JR.	LEX-0091-USA	5490

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EXAMINER
O HARA, EILEEN B

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 12/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/714,882	TURNER ET AL.	
	Examin r	Art Unit	
	Eileen B. O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with th c rrespond nc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 September 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-8 are pending in the instant application. Claims 1 and 2 have been amended and claims 7 and 8 have been added as requested by Applicant in Paper Number 11, filed Sept. 16, 2002.

Withdrawn Claim Objections

2. The objections to claim 1 are withdrawn in view of Applicants' amendment.

Withdrawn Rejections

3.1 The rejections of claim 1 under 112 § 2 are withdrawn in view of Applicants' amendment.

3.2 The rejections of claim 2 under 112 § 1 for written description is withdrawn in view of Applicants' amendment.

Specification

4. The objection to the title is maintained, because of the word "novel". To obtain a patent, an invention should be novel and the word is therefore redundant.

Claim Rejections - 35 USC § 101 and § 112

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

5. Claims 1-6 remain rejected, and new claims 7 and 8 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, for reasons of record in the previous Office Action, Paper No. 10, at pages 3-7, and below.

Applicants traverse the rejection and submit that the protein of the present invention NHP) is not identical to SEL-1, but is significantly more similar, 99.8% identity over the 506 amino acid overlap, to "Novel protein similar to SEL-1 (Sel-1 supressor of lin-12, *C. elegans*-like) (Accession Number Q9UGD3: Exhibit C and D). SEL-1 is the human homolog of C. elegans sel-1, which is an important regulator of the "notch" pathway. The Examiner agrees that based on this high degree of similarity, the protein of the instant invention and "Novel protein similar to SEL-1" are significantly more similar. Because of this similarity, the protein of the instant invention are probably the same protein, and are likely either splice variants, allelic variants, or differ in sequence because of sequencing errors. However, there is no disclosed or known activity for "Novel protein similar to SEL-1", as there is for human SEL-1. The protein of the instant invention and human SEL-1 are 46% identical, and based on this degree of homology, it is probably a Notch type ligand. However, human SEL-1 and the protein of the instant invention are 54% divergent, and it is not predictable that the protein of the instant invention and SEL-1 have the same activities or functions (such as binding to Notch).

Applicants argue that given their structural relatedness to Notch ligands, the described NHPs are suitable for use and modification as contemplated for other Notch ligands and antagonists.

Applicants' arguments have been fully considered but are not deemed persuasive. Though sequence homologies may provide information as to the family a protein may belong to, they still do not necessarily predict a function. Even 99% homology does not allow predictability, as evidenced by Yan et al., which discloses a ligand (EDA) that is present in two forms (EDA-A1 and EDA-A2, splice variants), the only difference being that one form has two extra amino acids. These two splice variants have completely different, non-overlapping specificities, and bind to two different receptors. These two ligands demonstrated distinctive temporal and spatial expression patterns in the developing hair follicles. Both are ligands and bind to receptors and therefore fall into the same class of protein, but the specific activity of one is different from the specific activity of the other. In the present case, the homology of the instant protein to the human SEL-1 protein is much less than 99%. The utility of any member of the Notch protein receptor and ligands family are not well-known in the art. As Applicants state on page 14 of the specification:

> Because of the diverse activities that have been associated with Notch signaling pathways, Notch receptors, and their associated ligands and antagonists have been subject to intense scientific scrutiny.

As opposed to a newly discovered DNA ligase, classifiying the protein of the instant invention as a member of the Notch ligand family does not automatically confer a specific and substantial utility to the protein, since there is diversity in the activities and biological functions of these ligands and associated receptors. Whereas a broad class of enzyme such as the DNA ligases have a general utility in such an application as ligation of DNA for cloning purposes and

which is essentially applicable to all of the members of that class, the class of proteins known as Notch ligands do not have a common practical utility which is based upon a property common to all of the members of that class, because the members of the Notch ligand family bind to different receptors and have diverse functions and biological activities.

Applicants argue that as the protein of the instant invention belongs to a family of compounds with a common, well established specific and substantial utility, the Federal Circuit's ruling in *In re Brana*, (34 USPQ2d 1436 (Fed.Cir.1995), "*Brana*") is completely on point, in which the Federal Circuit admonished the P.T.O. for confusing "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption. Applicants further submit that the Federal Circuit concluded that "[U]sefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development." And assert that even if, *arguendo*, further characterization might be required in certain aspects of the present invention, this does not preclude a finding that the invention has utility, as set forth by the Federal Circuit's holding in *Brana*. Applicants further present *In re Angstadt and Griffen*, *In re Angstadt and Griffen, supra;Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, and *In re Wands*, which address whether undue experimentation would be required to practice the claimed invention.

Applicants' arguments have been fully considered but are not deemed persuasive. The claimed invention and the issues in the instant application differ significantly from those in *In re Brana*. Brana et al. had filed an application directed to 5-nitrobenzo [de]isoquinoline-1,3-dione compounds for use as antitumor substances, which differed from several prior art compounds

due to the presence of a nitro group at one position on the compound and an amino or other amino group at a different position. In the prior art Paull et al. had disclosed similar compounds that had antitumor activity, and one of the similar compounds from Paull et al. "NSC 308847", had been found to have excellent activity against two specific in vivo murine tumor models. In addition to comparing the effectiveness of the claimed compounds of Brana et al. with that of the antitumor compounds disclosed in Paull et al., the specification of Brana et al. illustrated the cytotoxicity of the structurally similar claimed compounds of Brana et al. against human tumor cells in vitro, and concluded that these tests "had a good action." Brana et al. also supplied a declaration by Dr. Keilhauer, in which his tests indicated that the compounds of Brana et al. were far more effective as antitumor agents than structurally related antitumor agents disclosed in Zee-Cheng et al. when tested against two specific types of human tumor cells, HEp and HCT-29. The Federal Circuit concluded that these tumor models represented a specific disease against which the claimed compounds were alleged to be useful, and that the prior art and the declaration of Dr. Keilhauer supported the conclusion that one skilled in the art would be convinced of the applicants' asserted utility, even if some of the compounds were later found not to possess anti-tumor activity in human trials.

The compounds of Brana et al. were asserted to be antitumor agents, which have a specific, substantial and immediately testable activity, which are useful against a specific disease condition. In contrast, in the instant case, Applicants have asserted that the nucleic acids, encoded protein, and associated antibodies, agonists and antagonists can be used either diagnostically or therapeutically to identify and treat a wide spectrum of diseases or disorders such as Alzheimer's Disease, diabetes, stroke, vascular dementia, and conditions requiring

modulation of fat and cholesterol metabolism such as coronary artery disease. This is not a specific disease or disorder, but a wide variety of diseases or disorders that have a variety of etiologies. The instant application teaches that the protein is expressed in human testis cells and gene trapped human cell lines, among others, but does not teach what other cell types. One of ordinary skill in the art would not find it predictable, especially absent any working examples or guidance in the prior art, that a protein that is expressed in testis would be associated with vascular dementia or coronary artery disease. Additionally, the application of Brana et al. had working examples, cytotoxicity studies against human tumor cells in vitro, and additional later substantiation by a declaration showing antitumor action against two human tumor cell lines. This is in contrast to the instant situation, in which there is no working example of any kind, only assertions as to activity based on membership in a family of proteins. The issue is not that further characterization might be required – the compounds of Brana et al. would require further human clinical trials in order to determine effectiveness in humans. However, the compounds of Brana et al. had a specific asserted utility and could immediately be tested by methods known to one of ordinary skill in the art. This is not the situation in the instant case, in which extensive further research would be required to determine even if the polynucleotide and encoded protein of the instant invention were correlated with any type of disease or disorder.

Applicants further present case law presented on page 5 of the amendment, and submit that the threshold of utility is not high: an invention is 'useful' under section 101 if it is capable of providing some identifiable benefit, that to violate § 101 the claimed invention "must be totally incapable of achieving a useful result", that "any utility of the claimed compounds is

sufficient to satisfy 35 U.S.C. § 101", and "anything under the sun that is made by man" is patentable.

Applicants' arguments have been fully considered but are not deemed persuasive. 35 U.S.C. 101 reads as follows: Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title. Under the current Utility Examination Guidelines, Federal Register, Vol. 66, No. 4, pages 1092-1099, Friday, January 5, 2001, the term "useful" means that the invention must have a specific, substantial and credible utility, and guidance is provided by the Utility Examination Guidelines as to what constitutes a specific, substantial and credible utility.

Applicants assert that as just one example of the utility of the present nucleotide sequences, the claimed polynucleotide sequences can be used to track the expression of the genes encoding the described proteins, and in particular the specification describes how the described sequences can be represented using a gene chip format to provide a high throughput analysis of the level of gene expression. Applicants assert that the present sequences are specific markers of the human genome, such specific markers are targets for the discovery of drugs that are associated with human disease, and that the present nucleotide sequences would be an ideal, novel candidate for assessing gene expression using such gene chips. Applicants argue that such "DNA chips" clearly have utility, as evidenced by hundred of issued U.S. Patents, and that real world substantial utility of the present invention is provided by the fact that there is an entire industry established based on the use of gene sequences or fragments thereof in a gene chip format.

Applicants' arguments have been fully considered but are not deemed persuasive. *Any* expressed polynucleotide sequence can be used to track its expression, and this is not considered a specific and substantial utility. This *would* be a specific and substantial utility *if* the expression were specific for, for example, a particular cancerous state. This has not been demonstrated for the instant polynulceotide. Although gene chips are used in the pharmaceutical industry to discover, for example, alleles of genes associated with diseases or in drug discovery or toxicology studies, it is the entire array of genes or nucleic acid fragments that has utility, not any particular gene encoding a protein. The utility is based on the large number of sequences that can be screened at a time, and not any specific sequence within the gene chip. The more sequences that are screened, the more useful the information derived from gene chips. Applicants further argue that compositions that enhance the utility of such DNA chips must in themselves be useful. Again, *any* expressed polynucleotide can be used in such analyses, and so this is not a specific and substantial utility for the specifically claimed polynucleotide of the instant invention.

Applicants assert on page 6 of the amendment that the present nucleotide sequences clearly encode Notch ligands, the utility of which are described directly and by incorporation by reference of several U.S. Patents, 5,786,158, 5,780,300 and 5,856,441, which describe uses for the Notch proteins and ligands, and therefore, this evidence appears to support Applicants' assertion that Notch proteins, ligands and antagonists have well-recognized utility.

Applicants' arguments have been fully considered but are not deemed persuasive.

U.S. Patent No. 5,786,158 teaches that Notch proteins encoded by both human Notch homologs TAN-1 and hN were present at increased levels in the malignant part of the tissue

compared to the normal part, and the claims are drawn to methods of screening for malignancy based upon differential expression. However, while the protein of the instant invention may be in the same family, it is not the same protein, and absent evidence to the contrary, the polynucleotide of the instant invention is not differentially expressed in any malignancies. Therefore, the utility of the proteins in 5,786,158 is specific to those particular proteins, and not the family of proteins in general. The claims of U.S. Patent No. 6,333,167 are drawn to methods of evaluating a compound for the ability to inhibit proteolysis of a proteolytic substrate, one of which can be Notch receptor. In this case, Notch is being used as a general substrate because it can be cleaved by proteases, as are a number of other proteins. Therefore, this is not a specific and substantial utility for the Notch receptor. U.S. Patent No. 5,780,300 is drawn to methods of expansion of precursor cells comprising contacting the cells with an agonist of Notch function. However, the protein of the instant invention is *related* to the human SEL-1 protein, which is involved in Notch signaling, but there is no evidence that the protein of the instant invention is involved in Notch signaling. U.S. Patent No. 5,856,441 is drawn to the Serrate protein, a known Notch binding protein. Again, there is no evidence that the protein of the instant invention is involved in Notch signaling.

The assertion that the disclosed protein has biological activities similar to known Notch ligands cannot be accepted in the absence of supporting evidence, because the relevant literature reports examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities. For example, Tischer et al. (U.S. Patent 5,194,596) establishes that VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells,

which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). The differences between PDGF and VEGF are also seen *in vivo*, wherein endothelial-pericyte associations in the eye are disrupted by intraocular administration of PDGF but accelerated by intraocular administration of VEGF (Benjamin et al., 1998, Development 125:1591-1598; see Abstract and pp. 1594-1596). In the transforming growth factor (TGF) family, Vukicevic et al. (1996, PNAS USA 93:9021-9026) disclose that OP-1, a member of the TGF-β family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF-β family members BMP-2 and TGF-β1 had no effect on metanephrogenesis under identical conditions (p. 9023, paragraph bridging columns 1-2). See also Massague, who reviews other members of the TGF-β family (1987, Cell 49:437-8, esp. p. 438, column 1, second full paragraph to the end). Similarly, PTH and PTHrP are two structurally closely related proteins which can have opposite effects on bone resorption (Pilbeam et al., 1993, Bone 14:717-720; see p. 717, second paragraph of Introduction). Generally, the art acknowledges that function cannot be predicted based on structural information alone. For example, Bowie et al. (1990, Science 247:1306-1310) state that determination of three dimensional structure from primary amino acid sequence, and the subsequent inference of detailed aspects of function from structure is extremely complex and unlikely to be solved in the near future (p. 1306).

Applicants assert on pages 7-8 that an additional example of utility of the presently claimed polynucleotides is based on the fact that the claimed polynucleotide sequences define how the encoded exons are actually spliced together to produce an active transcription, and that the practical scientific value of expressed, spliced and polyadenylated mRNA sequences is

readily apparent to those skilled in the relevant biological and biochemical arts. Applicants submit the Venter et al. article which demonstrates the significance of expressed sequence information in the structural analysis of genomic data, and assert that the presently claimed polynucleotide sequences define biologically validated sequences that provide a unique and specific resource for mapping the genome. Applicants further assert that the usefulness of human genomic data, such as the presently claimed nucleic acid molecules, is substantial and credible and well-established, and that the test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable.

Applicants' arguments have been fully considered but are not deemed persuasive. The usefulness of human genomic data is substantial, credible and well-established. However, the usefulness is based upon all of the genomic data of all the expressed genes, and not just one gene. As in the gene chip example, this is not a specific and substantial utility for the specifically claimed polynucleotide of the instant invention.

Applicants further submit that polymorphisms identified in the sequences of the present invention provide significant and specific utility as taught in the specification, such as in the fields of forensic science and human population biology, and that such polymorphisms can also be used as specific markers for identifying human remains, determining group migration patterns and resolving issues of paternity, and that these utilities are credible and well established. Applicants' arguments have been fully considered but are not deemed persuasive. These uses are credible and well established, but any polymorphisms of any expressed gene can be used in

the same manner, so these are not considered specific and substantial utilities for the specifically claimed polynucleotide of the instant invention.

For the reasons above and those cited in the previous Office Action, the rejection is maintained.

Claims 1-6 also remain rejected, and new claims 7 and 8 are rejected under 35 U.S.C. 112, first paragraph, because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

It is believed that all pertinent arguments have been answered.

Conclusion

7. No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (703) 308-3312. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (703) 308-6564.

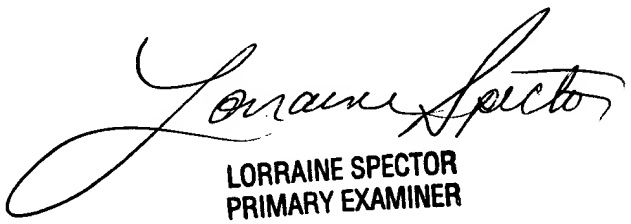
Official papers Before Final filed by RightFax should be directed to (703) 872-9306.

Official papers After Final filed by RightFax should be directed to (703) 872-9307.

Official papers filed by fax should be directed to (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Eileen B. O'Hara, Ph.D.



Patent Examiner